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Mitochondrial damage as a source of diseases and aging: a strategy of how to fight these

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Abstract

Some aspects of a defense against an oxidative stress are reviewed. All these aspects are focused on the necessity to defend mtDNA against damage. Protecting mechanisms involve the regulation of mitochondrial transport of nucleic acids, and the development of antioxygen defense as preventive measures. In the first case an exclusive role is supposed to play the mitochondrial benzodiazepine receptor and components, regulating the activity of its participants (mitochondrial porin and adenine nucleotide translocator). The possible transport of nucleic acids through Ca^{2+}-dependent permeability transition pore, representing one of the functional states of mitochondrial benzodiazepine receptor, is put forth. Such mechanisms can also cover the genomic nuclear–mitochondrial exchange. The second aspect reviews the possible complex of measures to lower the harmful effect of oxygen. Among these measures are mild uncoupling, the opening of a permeability transition pore and cellular apoptosis as was recently suggested by Skulachev. Problems such as cellular aging and mitochondrial diseases, are discussed in light of the relevance to the problem of oxidative stress.

Keywords: Mitochondrion; Aging; Degenerative disease; Mitochondrial DNA; Permeability transition pore; Mitochondrial channel; Oxidative stress

1. Introduction

The proven existence of two cellular pools of DNA raises many questions about the different roles played by cell nuclear and mitochondrial genetic material. Accumulated information in recent years showing increasing interaction of these intracellular DNA pools cannot be ignored and a comprehensive hypothesis explaining this interaction has yet to be proposed.

We have to admit that recent introduction and wide use of the term 'programmed cellular death' put some base for considering mitochondria as a control unit and some sort of biological clock with their own 'molecular clock' [1]. According to the latter, the mitochondrion can be regarded as a measuring device which keeps track of the temporal changes within a cell and the quantitative measures of their ticks are mutations in mtDNA. All these speculations result from the idea that mitochondria play an exclusive role in cellular aging and age-associated degenerative diseases. Basically these ideas arouse from the free radical theory of aging [2], or put differently, mitochondrial theory of aging.

2. Hypothetical mitochondrial exchange with nucleic acids

It is widely recognized that the mitochondrial function is that of oxidizing the cell substrates, thus producing a proton electrochemical potential and finally ATP. Very aggressive oxidative activity of mitochondria requires the proper protection of all intramitochondrial systems from being damaged. In spite of sophisticated defense (through the high activity of the enzymes trapping the radicals and highly reactive molecules) oxidative damage still does occur. Both for membranes and mtDNA the consequences of the resulting reactive oxygen species attack can be fatal.

The very high mutation rate of mtDNA (at least 10-times higher than in nuclear genome, including point mutation, deletion, insertion and depletion) is likely associated with more than one-hundred mitochondrial diseases, like my-

Abbreviations: mtDNA, mitochondrial DNA; PTP, permeability transition pore; ANT, adenine nucleotide translocator; MBR, mitochondrial benzodiazepine receptor; NA, nucleic acids; MRP RNAse, mitochondrial RNA-processing endonuclease.

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opathy, cardiomyopathy, encephalopathy, lactic acidosis, stroke-like episodes, epilepsy and many others. A new term 'mitochondrial medicine' has been introduced [3], commensurate with the importance of normal mitochondrial homeostasis in the maintenance of cellular functions. It has been suggested [4] that the DNA repair repertoire, which is less organized in mitochondria [5] than in the nuclei, is likely the source of at least some biologic dysfunction. The progression of mtDNA alterations is thought to be an aging process and when sufficiently advanced, the mtDNA mutations may result in cellular death.

There is an obvious intrinsic discrepancy. From one side, the aggressive intramitochondrial media makes mtDNA damage more probable and, from another, the mechanism of mtDNA repair is not as perfect as that in the nucleus. One may conclude that the frequency of mitochondrial mutations should be much higher than of nuclear DNA. If mitochondrial DNA is responsible for the aging process, the existing discrepancy must be revealed by a linear regression in terms of aging process and mortality of aging and diseases. The exponential nature of the mortality curve [6] apparently prompts that multiple reasons contribute to the aging as well as to mortality processes.

One can hypothesize that the relatively limited ability to repair the mtDNA lesions can be compensated for (or, on the other hand, be amplified) by equilibration of mitochondrial genetic material through its intermitochondrial exchange [7]. Analogous mechanisms are already well known in bacteria, where a general mechanism of the nucleic acids (NA) transport through bacterial membranes (during genetic transformation, transfection, viral infection and bacterial conjugation) has been described (for review, see [8]). The driving force for bacterial NA transport is postulated to be the proton electrochemical potential gradient (minus inside) [9]. Nucleic acids – which have a net negative charge – tend to leave the host cell and are transferred into extracellular medium or into the neighboring bacteria through the channels formed by tiny junctions (piles) between the cells. In case of conjugating bacteria the NA recipient would need to have lower membrane potential than that of the donor's cell to enable the transport.

There are numerous indirect observations supporting the idea of mitochondrial NA transport. Part of human mitochondrial DNA was found in the nuclear genome [10] (with the ability for autonomous replication [11]), as well as nuclear-encoded bovine 5S-rRNA [12] or mouse MPR RNA (mitochondrial RNA-processing endoribonuclease) were found in mitochondria [13] and other examples of nucleomitochondrial transport of NA. In this row is the recent finding of the fast dispersal of mitochondrial genetic material among the whole mitochondrial population, which is of fundamental importance [14]. The conclusion that the intermitochondrial exchange of their DNA (mtDNA) is a rapid, dynamic process is thus of prime importance.

The escape of DNA from yeast mitochondria has been described in detail [15]. A remarkable aspect of this was that the traffic from mitochondrion to nucleus was surprisingly high, but traffic in the opposite direction at least 100 000-fold less frequent. This supports the suggestion that the mitochondrial membrane potential may govern the process responsible for the apparently preferable unidirectional transport of negatively charged species outward from the mitochondria.

All mitochondrial channels described are probably too small to permit nucleoproteins transport through them without changing conformation of either the channel or NA. These are: 107 pS anion channel, MCC 1.3 nS megachannel, ATP-sensitive channel and low-conductance alkaline-induced channel in the inner membrane (for review see [16]). A much larger channel has been described in heart mitoplasts (up to 3.2 nS in 0.15 mM KCl) [17]. The outer mitochondrial membrane contains the only voltage dependent anion channel (mitochondrial porin, which in some features resembles the porin of the outer bacterial membrane).

It deserves to be specially considered the phenomenon of generation in mitochondria of so-called permeability transition pore (PTP) a water-filled channel with the size when up to 1.3 kDa molecules can go through. PTP can be induced by a number of factors with the obligatory participation of calcium ions (for reference see [18]). PTP has a specific inhibitor-cyclosporine A, a well known immunosuppressant. It is known to modulate its activity through the binding with a number of cyclosporine-binding proteins having the common name cyclophilins. Cyclophilins possess peptidyl-prolyl *cis–trans*-isomerase (rotamase) activity, implying their participation in three-dimensional organization of proteins. They are very abundant cellular proteins, having been found in cytosol, mitochondrial matrix and endoplasmic reticulum [19]. Cyclophilins were shown to be from the family of DNA-binding proteins (they can be released from DNA-containing affinity column) [20] and possess nuclease activity [21].

It has been speculated that mitochondrial PTP is highly regulated by the conformation of mitochondrial adenine nucleotide translocator (ANT), through the binding of cyclophilin to ANT. According to the scheme of Halestrap and Davidson [22] cyclosporine A, while bound to cyclophilin, removes it from ANT and the pore closes. Surprisingly, ANT has a high-affinity binding site for DNA [23]. Not only ANT, but all other members of the family of mitochondrial carriers have this knuckle – i.e., possess DNA-binding properties [24]. There is one more striking property of ANT, namely that it binds thyroid hormones with very high association constant of 2×10^{11} M^{-1} [25]. This suggests ANT could act as a thyroid hormone receptor [26].

The particular role in the process of mitochondrial transport of NA might play mitochondrial benzodiazepine receptor (MBR) [7]. The MBR is shown to be a multipro-

tein complex, consisting of an actual receptor 18 kDa subunit and two regulatory units, namely, mitochondrial porin and ANT [27]. Mitochondrial channel activity can be modulated by benzodiazepines, consistent with the idea that MBR is a mitochondrial channel [28]. If you add data, showing that the mitochondrial megachannel could be blocked by cyclosporine A [29], it seems to be clear that PTP is the functional state of MBR.

Thus multiple lines of evidence demonstrate that mitochondria possess all the necessary attributes for controlled machinery of NA transport: they have NA-binding proteins, transmembrane channels and potential sites of hormonal regulation. These features all potentially exist within the single structure MBR/PTP. Recent data show that the state of MBR/PTP determines the retention of added plasmid DNA by isolated mitochondria, as well as the release of mtDNA into incubation medium [30].

In discussing the possibility of mitochondrial transmembrane transport of NA one should not forget that mitochondria are very dynamic structures and able to exchange their content through the process of constant mitochondrial fission and fusion (where it takes place). In those cells, where ordered content does not permit intracellular mitochondrial motions (for example, in striated muscle) mitochondria might have some special features to enable intermitochondrial communications. They may be referred to intermitochondrial junctions, existing in striated muscle cells [31]. These intermitochondrial junctions were shown to be electrically permeable [32] and enriched with mitochondrial porin [33]. By the way, joining heart mitochondria within cardiomyocytes resemble conjugating bacterial cells [31,34] (Fig. 1), where the transfer of genetic material is well known.

It is clear, that understanding of the mechanisms of mitochondrial transmembrane transport of nucleic acids would help in directed repair of a damaged mitochondrial genome. The attempts to develop this kind of strategy have been made [35,36], through creating of a chimeric molecules, combining both oligonucleotides and mitochondrial protein signal sequences. Within this strategy, the machinery of the mitochondrial protein transport was intended to be use for the transfer of nucleic acids into mitochondria. At the same time, it is impossible to exclude that mitochondria possess their own transport machinery specific to oligonucleotides. This also seems to be the case for MRP RNA where the coding region has been deter-

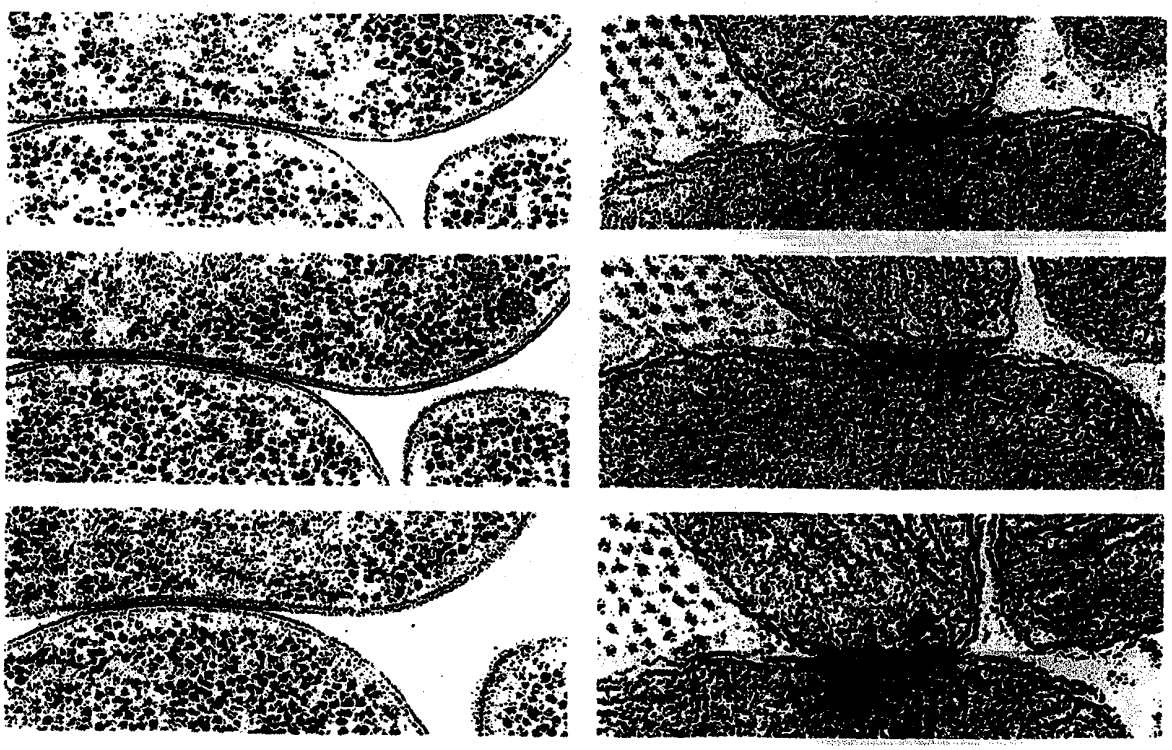

Fig. 1. Conjugational and intermitochondrial junctions. Left side – electron microscopic serial sections through conjugation-specific junctions in *E. coli* (from [34] with permission); right side – serial sections through the intermitochondrial junctions from rat heart muscle (from [31] with permission).

mined, and in which partial deletion results in the loss of mitochondria as a target for RNA transport [37]. HIV RNA is apparently using the same mode of transfer into mitochondria: 'by mistake' instead of MRP complex [38]. For both proteins and NA transport the participation of the same machinery with some modifications may be very possible. Recent data provide an evidence that for transport of nuclear-encoded RNA into yeast mitochondria, the energy source and intact machinery for protein transport are required (MOM19, MPII/MIM44 are necessary, although MOM72 is not) [39].

In a foregoing discussion we have already considered the necessity for 'protection' of mitochondrial genome from inevitable changes resulting in genomic mutation. The genome, if not properly repaired in time, can be the source of a number of mitochondrial diseases. Besides classical genome reparation, there are potentially some other ways to avoid such deleterious changes. One way may enable non-classical reparation through the possible NA exchange similar to that of bacteria. However, we cannot exclude the possibility, a priori, that such a NA exchange would actually result in the amplification of the genome damage through its spreading within the cell rather than serving to repair the damage. This idea finds a support from observations that mitochondrial DNA sequences that insert into the nuclear genome contribute to cancer and aging [10].

3. Skulachev's model of an antioxygen defense

Another way to limit a damage is by creating the conditions which limit the production of harmful oxygen intermediates. Fig. 2 schematically represents oxygen pathways, thus giving a strategy for mitochondrial antioxygen defense suggested by Skulachev [40].

One-electron reduction of oxygen in the respiratory chain results in the generation of superoxide anion radical, which beside of its own destructive properties, can induce the formation of even more destructive hydroxyl radicals. The last and other reactive oxygen species can induce lipid peroxidation, enzyme inactivation and DNA damage. Among these deleterious effects of oxygen, we choose and put on a scheme only mitochondrial DNA damage, which from our point of view is of prime importance.

There are two principle ways to protect the cell from an oxygen lesion. The first way is to prevent the formation of reactive oxygen species, and the second is to destroy

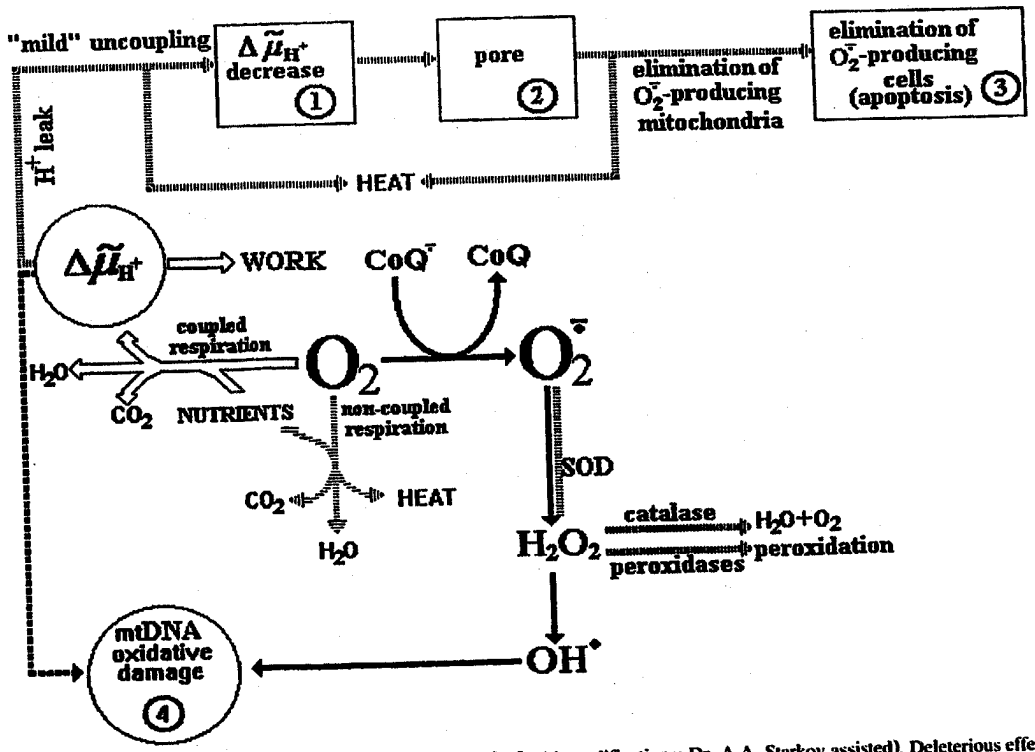

Fig. 2. Antioxygen defense mechanisms in mitochondria (by Skulachev [40] with modifications: Dr. A.A. Starkov assisted). Deleterious effects represented by solid lines, and antioxygen beneficial pathways, by normal dash. Bold-dashed lines represent supposed regulation of the activity of endonuclease activity by $\Delta\tilde{\mu}_{H^+}$.

already formed harmful oxygen intermediates. Conventional four-electron reduction of oxygen results in the generation of electrochemical potential of hydrogen ions in mitochondria. $\Delta\tilde{\mu}_H$· encircled in the scheme presented in Fig. 2 is used for ATP production and then for work. In State 4 the electron flow through the respiratory chain is low, and the rate of superoxide radical production is going up [41,42]. To redirect the process to the left of O_2, thus preventing the generation of reactive oxygen, the simplest way seems just to increase the load. Skulachev [40] suggests to induce a proton leak through the inner mitochondrial membrane which will result in higher oxygen consumption and production lowering of the long-lived $CoQ^{\cdot}$ level and, hence, of $O_2^{\cdot}$. Mild uncoupling (see block 1 in the scheme) is one of the ways to introduce a load to the system, thus discharging $\Delta\tilde{\mu}_H$·.

One more way to give a load to the system is the activation of any kind of work supported by ATPase. The beneficial effect of a physical load for recovery from many physiological disorders is well known. Here we can only mention the benefit of physical exercise for diabetic and elderly animals [43,44]. The mechanism of such a recovery may follow from the scheme (Fig. 2) according to which work will discharge the proton potential, thus making the oxygen danger less than when resting.

Block 2 (pore) represents the induction in mitochondria of a permeability transition pore. As it mentioned above, PTP, being the functional state of MBR, might serve as a root for the transport of NA in mitochondria [7,30]. According to Skulachev [40–42] mitochondrial PTP is the next step of antioxygen defense if the lesion is so severe that mild uncoupling is not enough to save a system from oxygen damage.

PTP-induced collapse of the membrane potential (which regulates a number of cellular functions) might be one piece in a multistep process of a programmed cellular death (apoptosis, represented by block 3 in Fig. 2) [17,18]. That is why PTP must have very precise regulation, not having to stay in an opened state longer than it is necessary for the recovery of mitochondrial functional properties; otherwise it is possible to initiate the mechanism of a cellular death. In this case optimal seems to be the oscillation of the mitochondrial membrane potential to prevent irreversible mitochondrial damage when the membrane potential has been lost for a long time. Definitely, it has some sense, if PTP has some physiological significance.

By the way, aging, is shown to sensitize mitochondria to Ca^{2+}-induced permeability transitions [45]. It may be that an aging process per se gives the signal that results in cellular death. If we discuss the aging phenomena in terms of mitochondrial changes, it becomes clear that mtDNA is constantly in conflict between the continual change of its 16569 nucleotide bases (for humans) and the necessity to keep the genome constant (shown as block 4 in Fig. 2). This conflict might be solved by a reasonable equilibrium between the rates of base change and the repair process. The last definitely includes intramitochondrial endonucleases, which should work in a very precise manner: their moderate activity deletes mutations [46], and anything beyond this moderate rate could result in irreversible mtDNA fragmentation [47]. What does optimize the activity of mitochondrial endonucleases? These enzymes are highly Mg^{2+}- and Ca^{2+}-dependent, and their activity definitely depends on the rate of oxidative phosphorylation [48]. We can only speculate that $\Delta\tilde{\mu}_H$· regulates the activity of mitochondrial endonucleases.

We cannot bypass the problem of protection from oxygen damage by using antioxidants, or by avoiding to introduce into the living system the elements initiating free-radical reactions (cf. [6]). Part of this problem is definitely of a nutritional nature. The same defensive effect can be achieved by the activation of radical scavengers – i.e., enzymes responsible for trapping oxygen intermediates (shown accompanied by dashed lines in Fig. 2 as superoxide dismutase, SOD, catalase, and peroxidases).

4. Conclusions

We have attempted to summarize the main measures designated to save mtDNA from oxidative damage. With this purpose in mind, we highlighted four blocks in Fig. 2, which, from our point of view, are of strategic importance. The regulation of a defense mechanism, directed to protect mitochondrial integrity from oxygen lesions, is following from the scheme, where the individual regulation of any of highlighted blocks takes place. The hypothetical NA transfer between mitochondria which proceeds through participation with a nucleus, potentially undermines the precise regulation of NA transfer. If it goes through MBR/PTP, all the factors determining the receptor's functional state can be involved. It seems to be that – at least in part – the participation of MBR/PTP, in all four problems is highly possible.

Acknowledgements

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